Kunkel on DNA Replication Fidelity

Understanding how DNA replicates itself, how errors occur during replication, and how these errors are sometimes repaired are keys to unlocking potential therapies for many kinds of cancer and perhaps the secrets to the vulnerability of HIV. In this year's G. Burroughs Mider Lecture, titled "DNA Replication Fidelity, Mismatch Repair, and Genome Stability," Thomas A. Kunkel, a research geneticist in the Laboratory of Molecular Genetics at the NIEHS, presented new research on these complex topics.

The G. Burroughs Mider Lectureship was established in 1968 by the NIH scientific directors to honor Mider for his distinguished NIH career including service as director of laboratories and clinics. The award is made annually to a scientist who has contributed to the biomedical research eminence of NIH.

Kunkel's research has provided some of the greatest understandings to date of how fidelity is achieved during DNA replication. In earlier years, analyses of the molecular basis of mutation were necessarily based on solely genetic measurements. Next, simplistic *in vitro* measurements were pursued. Finally, a system was developed that monitors the products of DNA synthesis *in vitro* using sophisticated reporter target molecules. This system, developed by Kunkel and the basis for much of the research presented in his lecture, and similar systems and extensions are now in use throughout the world.

As an adjunct to this system, Kunkel developed a means of recovering engineered DNA sequences with an efficiency so great that it made phenotypic screening unnecessary. This process has also come into widespread use, and its patent is a significant source of income for the NIH and for Kunkel's laboratory.

Kunkel has also made numerous other research contributions including uncovering a general mechanism of mutation in which both base mispairing and template slippage conspire to produce a mutation, which can consist of either a base pair substitution or a gain or loss of a base. He named this process "dislocation mutagenesis" and showed that it contributes significantly to the spectrum of spontaneous mutations. Kunkel also conducted an extended and continuing analysis of the reverse transcriptase of the human immunodeficiency virus. He showed this enzyme to be extraordinarily inaccurate, thereby explaining the basis for the rapid evolution of the virus in its host, and suggesting new points of therapeutic attack on AIDS. Over the past several years, Kunkel's group has developed a system to measure not only polymerase fidelity but also mismatch repair capacity in human cell extracts. Using this system, they have greatly extended the understanding of how mutations serve as progenitors of cancer.

Now that the structures of polymerases have been identified by crystallographers, Kunkel has established a number of collaborations to probe the molecular basis of polymerase fidelity. These structures predict numerous contacts between atoms of the polymerase and atoms of the DNA template and primer strands. Such contacts have spurred experiments that are already revealing the chemical mechanism of condensation and are just beginning to reveal the contacts that may be critical for fidelity. Engineered changes in the polymerases are now providing information about the control of fidelity by amino acid residues, not only at the active site but also far removed.

Kunkel joined the NIEHS as a senior staff fellow in 1982 and achieved tenure in 1986, only nine years after obtaining his doctorate degree. During this time he has trained numerous postdoctoral fellows who now occupy positions in academia around the country. "He has proved to be an outstanding mentor, giving full credit where due and closely promoting the personal and professional growth of his laboratory family," said John Drake, chief of the Laboratory of Molecular Genetics.

NIEHS Information

• **Envirohealth Clearinghouse**	100 Capitola Drive, Suite 108 Durham, NC 27713 USA phone: 1-800-643-4794 weekdays 9 A.M. to 8 P.M., EST FAX: 919-361-9408 e-mail: envirohealth@niehs.nih.gov
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NIEHS Scientist Serves at White House

Ronald Melnick, a toxicologist at the NIEHS, is serving a one-year assignment as an agency representative in the Environment Division of the White House Office of Science and Technology Policy, which has a primary role in advising the President and coordinating all science and technology policies and programs within the federal government.

Melnick is a group leader of the pharmacological and biomedical modeling group in the Laboratory of Quantitative and Computational Biology at the NIEHS. In his new assignment, Melnick works with the risk assessment subcommittee of the National Science and Technology Council's Committee on the Environment and Natural Resources (CENR) to develop and implement an intergovernmental risk assessment research strategy. The strategy sets priorities and coordinates federal research to strengthen the scientific basis of environmental risk assessment to more effectively guide public health decisions.

Working with the CENR, Melnick has had a major role in the preparation of an interagency assessment of potential health risks associated with oxygenated gasoline. "The NIEHS is especially glad to have Dr. Melnick serving in this role. It is most important that the research that the institute is doing, and the expertise of its staff, be applied to these major policy questions in a timely way," said Kenneth Olden, director of NIEHS.